(150 mg., m.p. 260°) were collected. Recrystallization from hot water gave colorless prisms, m.p. 260°. *Anal.* Calcd. for $C_5H_4O_3N_2 \cdot H_2O$: C, 37.98; H, 3.83; N, 17.72. Found : C, 38.48; H, 4.01; N, 17.91. This was identified with an authentic sample prepared according to the method of Homer *et al.*[4] by comparison of their IR spectra.

The authors express their gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo and Dr. K. Takeda, Director of this laboratory, for their helpful guidance and encouragement. Thanks are also to Dr. T. Kubota, Dr. Y. Matsui, Mr. I. Tanaka and Mr. M. Takasuka for ultraviolet and infrared spectral measurements, and to I. Ishizuka for carrying out gas chromatography, and to the members of the Analysis Room of this laboratory for elemental analysis.

Summary

3-Methylpyridazine 1-oxide (II) and 2-oxide (III) were separated from the N-oxidation products of 3-methylpyridazine (I). Nitration of II could not be accomplished, but III gave 3-methyl-mononitropyridazine 2-oxide (VI) in good yield. The nitro group of VI was proved to be in 5-position. Reaction of 3-methyl-6-methoxypyridazine 2-oxide (IX) with phosphoryl chloride gave 3-methyl-5-chloro-6-methoxypyridazine (XIX) and with acetic anhydride gave 6-methoxy-3-pyridazinemethanol acetate (XXI).

(Received January 17, 1962)

UDC 547.852.2

8. Masaru Ogata and Hideo Kano : Pyridazines. II.[*1]
4-Methylpyridazine N-Oxides.

(*Research Laboratory, Shionogi & Co., Ltd.*[*2])

In the first paper of this series,[*1] it was reported that N-oxidation of 3-methylpyridazine gave two isomeric mono-N-oxides, i. e. 3-methylpyridazine 1-oxide (I) and 2-oxide (II). Some reactions of these N-oxides were also investigated. It seemed of interest to study the preparation of other two possible, but unknown methylpyridazine mono-N-oxides, 4-methylpyridazine 1-oxide (IV) and 2-oxide (V).

The present paper deals with the synthesis and nitration of these two N-oxides.

Heating of 4-methylpyridazine (III) with hydrogen peroxide in glacial acetic acid at 70° for 6 hours, gave a product. By gas chromatographic procedure, the product gave two distinct peaks, one of which was much larger than the other as indicated in Fig. 1. There was no evidence of decomposition of the product on the column, so the product must be a mixture of two compounds. A small amount of crystals was separated from the reaction product, which was recrystallized from the benzene to yield a mono-N-oxide IV, m.p. 83~84°, UV λ_{max}^{EtOH} mμ (log ε) : 266 (4.05), 314 (3.61), IR : ν_{N-O} 1328 cm^{-1} (CS_2). The filtrate was chromatographed on alumina and the column was eluted with benzene and chloroform. The fraction eluted with benzene gave, after distillation under reduced pressure, another mono-N-oxide V, b.p_4 135°, UV λ_{max}^{EtOH} mμ (log ε) : 265 (4.01), 305 (3.52), IR : ν_{N-O} 1322 cm^{-1} (CS_2).

In order to deduce the structure of these isomeric 4-methylpyridazine N-oxides, the following experiments were carried out. 4-Methyl-3(2*H*)-pyridazinone (VIII), m.p. 165~166°, and 5-methyl-3(2*H*)-pyridazinone (IX), m.p. 160~161°, were synthesized according to the procedure of Takabayashi.[1] The melting point of VIII did not agree with

---

*1 Part I : This Bulletin, **11**, 29 (1963).
*2 Fukushima-ku, Osaka (尾形 秀, 加納日出夫).
1) N. Takabayashi : This Bulletin, **5**, 229 (1957).

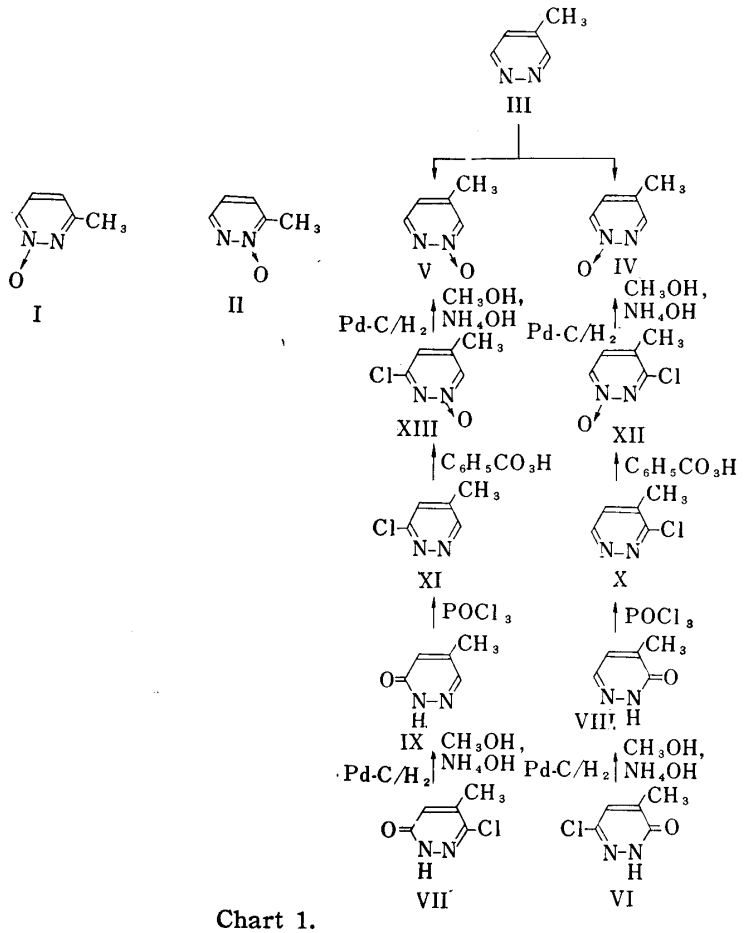

Chart 1.

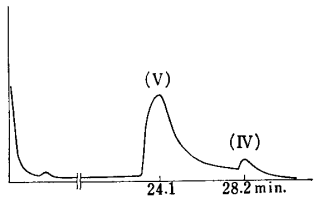

Fig. 1. Gas Chromatography of 4-Methylpyridazine N-Oxides

Conditions : Thermol-2(Shimadzu), 3 m. × 6 mm., column, at 180°, H_2 flow rate 200 cc./min.

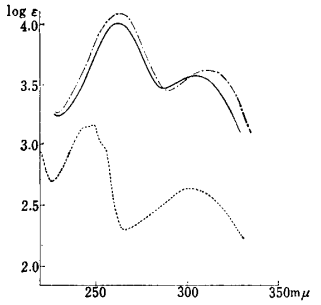

Fig. 2. Ultraviolet Absorption Spectra (in EtOH)

..... III
– – – – – IV
——— V

that reported by Takabayashi, but IX was identical with his sample*3 by comparison of their infrared absorption spectra, VIII and IX were treated with phosphoryl chloride to give 3-chloro-4-methylpyridazine (X) and 6-chloro-4-methylpyridazine (XI) respectively. These chloro compounds X and XI were oxidized with perbenzoic acid in chloroform to give 3-chloro-4-methylpyridazine N-oxide (XII) and 6-chloro-4-methylpyridazine N-oxide (XIII) respectively. Catalytic hydrogenation of XII and XIII with palladium-carbon

*3 This sample was sent from Dr. N. Takabayashi of the University of Toyama, to whom authors wish to express thanks.

in hydrous methanolic ammonia solution gave 4-methylpyridazine N-oxide (IV) and (V) respectively, each of which was identical with the sample prepared from III by N-oxidation.

N-oxidation of 3-chloropyridazine or 3-methyl-6-chloropyridazine gives only the sole N-oxide, in which the oxygen atom is attached to the nitrogen atom at the *meta*-position to the chloro group.*[1~3] These facts support that XII is 1-oxide and XIII is 2-oxide, accordingly IV derived from XII is 1-oxide and V from XIII is 2-oxide. This assumption will be confirmed with the dipolemoment studies in Part III of this series.

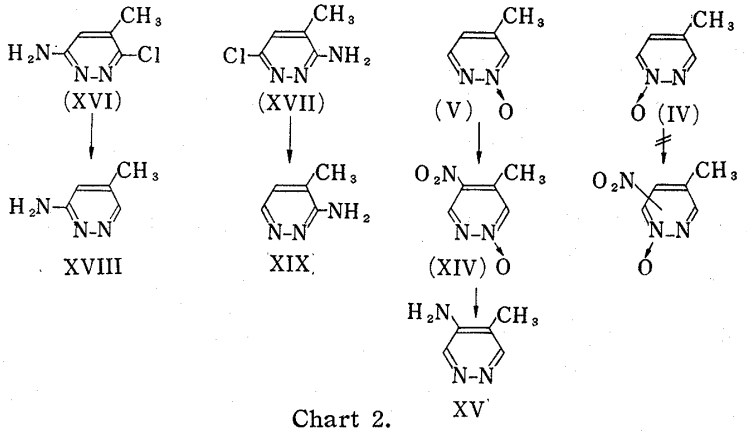

Chart 2.

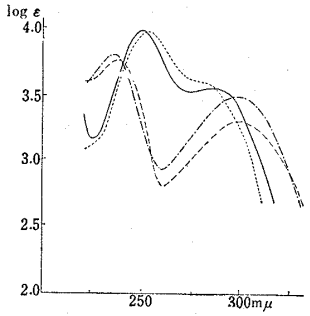

Fig. 3. Ultraviolet Absorption Spectra (in EtOH)

——— XV
– – – – XVIII
– – – – – XIX
····· 3-Methyl-5-aminopyridazine

In order to compare the reactivity of IV and V, nitration of these compounds was investigated. By heating of IV with fuming nitric acid and sulfuric acid at 100° for 6 hours the unchanged IV was recovered. On the other hand, the same treatment with V gave a mononitro compound XIV. Catalytic hydrogenation of XIV with palladium-carbon in methanolic hydrochloric acid afforded 4-methyl-monoaminopyridazine (XV). XV was not identical with both 6-amino-4-methylpyridazine (XVIII) and 3-amino-4-methylpyridazine (XIX), which were derived from the corresponding chloro compounds, XVI and XVII. Ultraviolet absorption spectrum of XV was quite different from XVIII and XIX, and very similar to 3-methyl-5-aminopyridazine as shown in Fig. 3. From these results, XV was formulated as 4-methyl-5-aminopyridazine. Consequently XIV was decided to be 4-methyl-5-nitropyridazine 2-oxide.

Experimental*[4]

4-Methylpyridazine 1-Oxide (IV) and 2-Oxide (V)——A mixture of 4.6 g. of 4-methylpyridazine (III), 30 cc. of glacial AcOH and 15 cc. of 30% H_2O_2 was heated at 70° for 3 hr., further 15 cc. of 30% H_2O_2

*[4] M.p.s were determined on a Kofler-Block "Monoscope IV" and uncorrected.

2) H. Igeta : This Bulletin, 8, 559 (1957).

3) H. Kano, M. Ogata, H. Watanabe, I. Ishizuka : *Ibid.* **9**, 1017 (1961).

was added, and again heated at the same temperature for 3 hr. To this solution, 30 cc. of water was added, AcOH was evaporated under a reduced pressure, and this procedure was repeated. After neutralization of the residue with Na_2CO_3, the solution was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and evaporated. A small amount of benzene was added to the residue, and the mixture was allowed to stand for one day in a cool place. The separated crystals were recrystallized from benzene to 400 mg. of colorless prisms V, m.p. 83~84°. *Anal.* Calcd. for $C_5H_6ON_2$: C, 54.54; H, 5.49; N, 25.44. Found : C, 54.36; H, 5.93; N, 25.18.

The filtrate was chromatographed on alumina (20 g.), and the column was eluted with benzene. The initial 40 cc. of eluate was collected and benzene was evaporated. The residue was distilled under reduced pressure to yield 1.9 g. of colorless oil V, $b.p_4$ 135°, which was solidified as hygroscopic crystals on cooling. *Anal.* Calcd. for $C_5H_6ON_2$: C, 54.54; H, 5.49; N, 25.44. Found : C, 54.34; H, 5.64; N, 25.89.

4-Methyl-3(2*H*)-pyridazinone (VIII)——A mixture of 2 g. of VI, 50 cc. of MeOH, 5 cc. of 28% NH_4OH and 0.5 g. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 per mole of VI was absorbed. The catalyst was filtered, the solvent removed and the residue was extracted with AcOEt. AcOEt was evaporated. The residue was recrystallized from AcOEt to give 1.2 g. of colorless prisms, m.p. 165~166°. *Anal.* Calcd. for $C_5H_6ON_2$: C, 54.54; H, 5.49; N, 25.44. Found : C, 54.74; H, 5.47; N, 25.12.

5-Methyl-3(2*H*)-pyridazinone (IX)——A mixture of 4 g. of VII, 100 cc. of MeOH, 10 cc. of 28% NH_4OH and 1.5 g. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 per mole of VII was absorbed. When the reaction mixture was treated in the same way as described above, 2.95 g. of IX as colorless prisms, m.p. 160~161° was obtained. *Anal.* Calcd. for $C_5H_6ON_2 \cdot H_2O$: C, 46.87; H, 6.29; N, 21.87; H_2O, 14.07. Found : C, 47.39; H, 6.35; N, 21.67; H_2O, 14.21.

3-Chloro-4-methylpyridazine (X)——A mixture of 0.9 g. of VIII and 5 cc. of $POCl_3$ was heated on a water bath for 0.5 hr. The $POCl_3$ was distilled off under reduced pressure, and the residual oil was poured onto ice with stirring. The solution was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. The extract was dried, evaporated, and the residue was sublimated under reduced pressure. Recrystallization from cyclohexane gave 0.72 g. of colorless leaflets, m.p. 46~47°. *Anal.* Calcd. for $C_5H_5N_2Cl$: C, 46.69; H, 3.88; N, 21.79. Found : C, 46.72; H, 4.07; N, 22.00.

6-Chloro-4-methylpyridazine (XI)——A mixture of 0.8 g. of IX and 4 cc. of $POCl_3$ was heated on a water bath for 0.5 hr. When the reaction mixture was treated in the same way as described above, 0.35 g. of XI as colorless prisms, m.p. 33°, was obtained. Recrystallization from petr. benzin gave colorless needles, m.p. 33°. *Anal.* Calcd. for $C_5H_5N_2Cl$: C, 46.69; H, 3.88; N, 21.79. Found : C, 46.68; H, 4.02; N, 22.01.

3-Chloro-4-methylpyridazine 1-Oxide (XII)——A mixture of 500 mg. of VIII and 2 cc. of $POCl_3$ was heated on a water bath for 0.5 hr., and excess of $POCl_3$ was removed under reduced pressure. The reaction mixture was poured onto ice, neutralized with Na_2CO_3, and extracted with $CHCl_3$ (30 cc.). The $CHCl_3$ layer was added with 20 cc. (containing 1.5 g. of perbenzoic acid) of $CHCl_3$ solution. The solution was allowed to stand for 2 days at room temperature and $CHCl_3$ was removed under reduced pressure. H_2O was added to the residue, neutralized with $NaHCO_3$, and then extracted with $CHCl_3$. $CHCl_3$ was evaporated. The residue was recrystallized from benzene to colorless needles, m.p. 148~149°. Yield, 200 mg. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.52; H, 3.46; N, 19.31. Found : C, 41.74; H, 3.58; N, 18.87.

3-Chloro-5-methylpyridazine 1-Oxide (XIII)——A mixture of 900 mg. of IX and 4 cc. of $POCl_3$ was heated on a water bath for 0.5 hr. When the reaction mixture was treated in the same way as described above, 570 mg. of XIII as colorless needles, m.p. 127~128° was obtained. *Anal.* Calcd. for $C_5H_5ON_2Cl$: C, 41.52; H, 3.46; N, 19.31. Found : C, 41.74; H, 3.58; N, 18.87.

Catalytic Reduction of 3-Chloro-5-methylpyridazine 1-Oxide (XII) : Formation of 4-Methylpyridazine 1-Oxide (IV)——A mixture of 250 mg. of XII, 10 cc. of MeOH, 1 cc. of methanolic NH_3 and 0.1 g. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 per mole of XII was absorbed. The catalyst was filtered, and MeOH was evaporated. The residue was recrystallized from benzene to colorless prisms, m.p. 79~80°. Yield, 70 mg. This product was recrystallized repeatedly from benzene to colorless prisms, m.p. 83~84°. This was identified with IV derived from III by comparison of their IR spectra.

Catalytic Reduction of 3-Chloro-5-methylpyridazine 1-Oxide (XIII) : Formation of 4-Methylpyridazine 1-Oxide(V)——A mixture of 300 mg. of XIII, 10 cc. of MeOH, 1 cc. of methanolic NH_3 and 0.1 g. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 per mole of XIII was absorbed. The catalyst was filtered, and MeOH was evaporated. The residue was distilled under reduced pressure to colorless oil. Yield, 50 mg. This was identified with V derived from III by comparison of their IR spectra.

4-Methyl-5-nitropyridazine 2-Oxide (XIV)——To a cold solution of V in 2 cc. of conc. H_2SO_4, 15 cc. of fuming HNO_3 was added slowly, and the mixture was heated on a boiling water bath for 6 hr.

The mixture was poured onto ice, extracted with $CHCl_3$, $CHCl_3$ was distilled off and the residue was recrystallized from MeOH to yellow prisms, m.p. 144~145°. Yield, 65 mg. *Anal.* Calcd. for $C_5H_5O_3N_3$: C, 38.71; H, 3.25; N, 27.05. Found : C, 38.80; H, 3.36; N, 26.65.

4-Methyl-5-aminopyridazine (XV)——A mixture of 200 mg. of XIV, 2 cc. of MeOH, 1 cc. of 10% HCl-MeOH and 0.1 g. of 10% Pd-C was subjected to hydrogenation. Four moles of H_2 per mole of XIV were absorbed. The catalyst was filtered, the filtrate was neutralized with methanolic NH_3 solution, and the solvent was evaporated. The residue was extracted with AcOEt. AcOEt was evaporated. The residue was recrystallized from AcOEt to give 50 mg. of colorless prisms, m.p. 137~138°. *Anal.* Calcd. for $C_5H_7N_3 \cdot \frac{1}{2}H_2O$: C, 50.83; H, 6.83; N, 35.57; H_2O, 7.61. Found : C, 50.54; H, 7.01; N, 35.10; H_2O, 8.01.

3-Amino-5-methylpyridazine (XVIII)——A mixture of 700 mg. of XVI, 10 cc. of MeOH, 2 cc. of methanolic NH_3 and 0.1 g. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 per mole of XVI was absorbed. The catalyst was filtered, the solvent was removed and the residue was extracted with AcOEt. AcOEt was evaporated. The residue was recrystallized form AcOEt to yield 300 mg. of colorless prisms, m.p. 183~184°. *Anal.* Calcd. for $C_5H_7N_3$: C, 55.03; H, 6.47; N, 38.51. Found: C, 55.13; H, 6.57; N, 38.22.

4-Amino-4-methylpyridazine (XIX)——A mixture of 1.0 g. of XVII, 10 cc. of MeOH, 2 cc. of methanolic NH_3 and 0.2 g. of 10% Pd-C was subjected to hydrogenation. When the reaction mixture was treated in the same way as described above, 500 mg. of XIX as colorless prisms, m.p. 200°(decomp.) was obtained. *Anal.* Calcd. for $C_5H_7N_3$: C, 55.03; H, 6.47; N, 38.51. Found : C, 55.03; H, 6.49; N, 38.68.

The authors express their gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo and Dr. K. Takeda, Director of this laboratory, for their helpful guidance and encouragement. Thanks are also to Dr. T. Kubota, Dr. Y. Matsui, Mr. I. Tanaka and Mr. M. Takasuka for ultraviolet and infrared spectral measurements, and to I. Ishizuka for carrying out gas chromatography, and to the members of the analysis room of this laboratory for elemental analysis.

Summary

4-Methylpyridazine 1-oxide (IV) and 2-oxide (V) were synthesized from 4-methylpyridazine (III). Nitration of IV could not be accomplished, but V gave 4-methyl-mononitropyridazine 2-oxide (XIV) in low yield. The nitro group of XIV was proved to be in 5-position.

(Received January 17, 1962)

UDC 547.852 : 543.226

9. Haruyuki Watanabe, Masaru Ogata, and Hideo Kano : Pyridazines. III.[1,2] The Dipole Moments and the Structures of Monomethylpyridazine N-Oxides.[3]

(*Research Laboratory, Shionogi & Co., Ltd.*[*1])

In the foregoing papers of this series,[1,2] the synthesis of all possible monomethylpyridazine N-oxides, namely 3-methylpyridazine 1-oxide (IV), 2-oxide (III), 4-methylpyridazine 1-oxide (IX) and 2-oxide (XII) were reported. The structures of two isomeric 3-methylpyridazine N-oxides (IV and III) were established, however, those of two 4-methylpyridazine N-oxides (IX and XII) were presumed only by analogy.

---

*1 Fukushima-ku, Osaka (渡辺春幸, 尾形 秀, 加納日出夫).

1) Part I : M. Ogata, H. Kano : This Bulletin, **11**, 29 (1963).
2) Part II : *Idem* : *Ibid.*, **11**, 35 (1963).
3) A preliminary report of a part of this work was published as the Communication to the Editor in this Bulletin **9**, 1017 (1961).